Remarks

Claims 1-4, 6-13, 16, 17, 20-28 are pending in this application. Claims 6 and 27 are amended. No new matter is added, and the amendments do not necessitate further search or examination. The amendments are exclusively to add clarity and consistency to the nomenclature of the specification and claims, in accordance with the well understood terms of art "msr" and "msd".

Withdrawal of Rejections Under 35 U.S.C. § 102

Applicant thanks Examiner Shen for withdrawing the rejection of claims 1, 3, 4, 22, and 23 under 35 U.S.C. § 102(e).

Rejections Under 35 U.S.C. § 112

Claims 6, 8, 9, 10, 11, 12, and 24-28 were rejected under 35 U.S.C. 112, second paragraph. Applicant respectfully notes that this objection was raised for the first time in the most-recent Final Action, and relates to language in claim 6, and its dependent claims, which is original claim language. In particular, claim 6 formerly recited "*an msr coding region encoding an msr element and an msd coding region encoding an msd element.*" As amended, claim 6 recites "*an msr coding region encoding an RNA component of the gene targeting substrate called an msr element and an msd coding region encoding ~~an~~ a DNA component of the gene targeting substrate called an msd element.*"

Applicant acknowledges that the nomenclature of the claimed constructs is somewhat complex, in that the mechanism of the invention involves transformation with a gene targeting construct that is transcribed to form a gene targeting message RNA, which in turn is reverse transcribed in a self-primed reaction to form a gene targeting substrate that may comprise both DNA and RNA components. Paragraph 0045 has been editorially amended to introduce additional consistency to the use of the relevant terms. In addition, the nature of "msr" and "msd" elements is discussed throughout the specification, for example at paragraph 17 on page 6, as follows (with emphasis added):

> Retrons have been known for some time as a class of retroelement, first discovered in gram-negative bacteria such as *Myxococcus xanthus, Stigmatella aurantiaca* and *Escherichia coli*. Retrons mediate the synthesis in host cells of multicopy single-stranded DNAs (msDNA), which typically include a DNA component and an RNA component. The native msDNA molecules reportedly exist as single-stranded DNA-RNA hybrids, characterized by a structure which comprises a single-stranded DNA branching out of an internal guanosine residue of a single-stranded RNA molecule at a 2',5'-phosphodiester linkage. **Native retrons have been found to consist of the gene for reverse transcriptase (RT) and an msr-msd region under the control of a single promoter. The msd region typically codes for the DNA component of msDNA, and the msr region typically codes for the RNA component of msDNA. In some retrons, the msr and msd genes have overlapping 3´ ends, and are oriented opposite one another with a promoter located upstream of msr which transcribes through the msd-msr region. The msd-msr region generally contains two inverted repeat sequences, designated "a" and "b", which together make up a stable stem structure in msDNAs. The single RNA transcript from the msr-msd region serves not only as a template for reverse transcription but, by virtue of its secondary structure, also serves as a primer for msDNA synthesis by a reverse transcriptase.**

The first objection raised to the "msr" and "msd" terms is that the specification does not disclose what "msr" and "msd" stand for. It is respectfully submitted that the foregoing paragraph, and the remainder of the specification, including paragraph 0045 as amended, do in fact disclose in sufficient detail what "msr" and "msd" stand for. In particular, it is respectfully submitted that a person of ordinary skill in the art could determine the meaning of these terms with adequate specificity, in view of the mechanistic purposes of the invention (see *Howmedica Osteonics Corp. v. Tranquil Prospects, Ltd.*, 401 F.3d 1367, 1371 (Fed. Cir. 2005) (claim not indefinite due to ambiguity when meaning readily ascertained from the description in the specification); *Personalized Media Communications, LLC v. Int'l Trade Comm'n,* 161 F.3d 696, 705 (Fed. Cir. 1998), and see generally *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir.

2005) (en banc) (claims are construed in the context of the specification and prosecution history, as they would be understood by persons in the same field of endeavor)).

In raising the second objection under 35 USC 112 to the "msr" and "msd" terms, the Action refers to paragraph [0101], which reads as follows:

> iii) a nucleotide sequence encoding a reverse transcriptase (RT). The nucleotide sequence may comprise, in the following order, an msr element ORF, a gene-targeting nucleotide sequence, and an msd element ORF (as shown in FIG. 1), and is referred to herein as "msr-GTNS-msd". Alternatively, the GTNS may be inserted within the msd region, preferably within a hairpin region of msd (see for example FIGS. 4, 3B, 5). In alternative embodiments, the msr and msd regions may be modifed (inverted) as shown in FIG. 11 so that the 3' msr, and 5' msd, termini are spatially separated from the internal rG residue used to prime the synthesi of msDNA. In this manner foreign inserts may added to the 5' ends of msd. Synthesis of msDNA (gene targeting susbtrate; GTS) has been observed using the constructs outlined in FIG. 3B, 5 (modified msd hairpin), as shown in FIG. 6 and 7. Similarly, synthesis of a GTS has been observed using constructs shown in FIG. 11 (inverted msr-msd regions) as shown in FIGS. 12 and 13.

The Action specifically suggests that in this paragraph the phrases "*msr element*" and "*msd element*" appear to be specific DNA sequences. Applicant notes that the relevant phrases are actually "*msr element ORF*" and "*msd element ORF*", which in context clearly refers to an msr or msd coding region, i.e. an open reading frame encoding an msr element or msd element.

Rejections Under 35 U.S.C. § 103

Claims 1, 3, 4, 7, 10, 13, 16, 17, and 20-23 stand rejected under 35 U.S.C. § 103(a) over Conrad et al. (US 2003/0082800 A1) in combination with Levin (*Mol. Cell Biol.* 15(6):3310-7, 1975). The Action acknowledges that Conrad et al. do not teach a message RNA that self-primes reverse transcription.

The Examiner relies on the Levin reference for teaching a self-priming mechanism and asserts that it would have been obvious to use this self-priming construct for gene targeting. It is respectfully submitted that there is nothing in Levin that would provide a reasonable basis for an expectation that the self-priming construct that is disclosed therein would provide an adequate degree of expression for the purposes for gene targeting. In particular, on page 3315 of Levin, second column, Levin goes to some length to describe the uncertainties associated with the putative self-priming mechanism described therein, including discussing the possibility that particular enzymatic activities might be required for that mechanism to operate. Given the relevant uncertainties, in the absence of an illustration that self-priming mechanisms are capable of mediating adequate reverse transcription for gene targeting, there is no basis in the cited art for one to expect that the putative mechanism of Levin could be used in gene targeting.

Applicant respectfully submits that the Anderson and Schaefer references fail to satisfy the requirements for a finding of obviousness of claims 1, 3, 4, 7, 10, 13, 16, 17, and 20-23 , in accordance with the requirements of the "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" (Federal Register, Vol. 72, No. 195, Oct. 10, 2007, pp. 57526 – 57535) (the "Guidelines"). In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 at 17-18 (1966), the Supreme Court set out the following objective framework for applying the statutory language of §103:

> "Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."

Accordingly, the Guidelines confirm that obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court in *Graham* are as follows:

(1) Determining the scope and content of the prior art;

(2) Ascertaining the differences between the claimed invention and the prior art; and

(3) Resolving the level of ordinary skill in the pertinent art.

With respect to the second of the *Graham* factual inquiries, Applicant respectfully submits that important differences exist between the claimed invention and the cited references. In particular, there is no teaching or suggestion in Levin to the effect that the self priming mechanism disclosed therein is capable of functioning with an extrinsic gene targeting nucleotide sequence that is homologous to a target locus. Much less is there any indication that the product of a self primed reverse transcription reaction, using that self-priming mechanism, would be capable of mediating insertion, deletion or substitution of one or more bases of the sequence of the target nucleic acid. In fact the self-priming mechanism of Levin is elucidated by showing that the sequences involved in self priming are sensitive to various mutations; there is accordingly no suggestion that the mechanism disclosed therein is sufficiently robust to tolerate manipulation for the purposes of generating an effective gene targeting vector. Also, the putative mechanism of Levin requires pairing between 3' and 5' sequences of an mRNA, suggesting that alternations in the intervening sequences might well have an effect on the efficiency of priming.

Applicant further respectfully notes that these differences are significant, because they dictate that there could have been no reasonable expectation that the putative self priming mechanism of Levin could be made to work as an adaptation of the expression vectors of Conrad et al.. In this context, Applicant notes that Conrad et al. was filed approximately 7 years after the publication of Levin, and there is no suggestion in Conrad that the alternative priming mechanisms of Levin were optional components of the constructs disclosed therein. Thus, in view of the above differences, Applicant respectfully submits that the second of the three *Graham* factual inquiries strongly supports a finding of non-obviousness.

The Guidelines provide a number of potential, non-exclusive, rationales for supporting a finding that a claimed invention is obvious (with emphasis added):

- combining prior art elements **according to known methods** to yield **predictable** results;
- simple substitution of one known element for another to obtain **predictable** results;
- use of known technique to improve similar devices (methods, or products) in the same way;
- applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- "obvious to try" - choosing from a finite number of identified, **predictable** solutions, **with a reasonable expectation of success**; and
- known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been **predictable** to one of ordinary skill in the art.

The emphasis in the Guidelines is accordingly the **predictability** of the combination, as a basis for a finding that there is a reasonable expectation of success associated with a prior art combination. It is respectfully submitted that in the present case, there is no such element of predictability in the purported combination of prior art, and accordingly no reasonable expectation of success.

With respect to claims 7 and 10, the Action suggests that because the reverse transcriptase of Conrad et al. is synthesized in the cytoplasm and transported into nuclei, the RT must either have been transported into nuclei by the present of its own NLS or by association with other nuclear proteins with a NLS. With respect, there is no disclosure in Conrad et al. to the effect that the RT activity required for that method is present in the nucleus. In fact, reverse transcription in Conrad et al. requires the presence of a tRNA primer, suggesting the RT is in fact active in the cytosol. There is in fact no instance of any of the words "nucleus", "nuclear" or "nuclei" in Conrad et al. It is accordingly submitted that there is no disclosure in Conrad upon which to fairly impute that it discloses or even suggests a reverse transcriptase having a nuclear localization signal sequence.

Applicant further respectfully submits that neither the first nor the third of the *Graham* factual inquiries detracts from a finding of non-obviousness in the present case. Applicant therefore respectfully submits that the subject-matter defined by the claims would not have been obvious to one of ordinary skill in the art upon consideration of all of the relevant facts, and respectfully requests that the rejections under 35 U.S.C. § 103(a) be withdrawn.

Conclusions

Based on the forgoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at (503) 595-5300.

Respectfully submitted,

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